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Pain measurement

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Increasing evidence from laboratory methods in humans and animals indicates that pain arises from, and is modulated by, a number of mechanisms. In addition, these mechanisms are not static but change as pain persists. Recent human studies have demonstrated new aspects of pain processing at all levels of the central nervous system. Studies of the influence of analgesic agents on a large number of experimental pain measures have shown a preferential effect of opioids for attenuating the central integration of prolonged stimuli while local anesthetics may be more effective for brief stimulation. Studies of NK1 antagonists in man have shown results similar to those found with animals. There is little effect on brief stimulation of Aδ and C-fiber nociceptors, including conditions that can evoke central summation. However, these antagonists, which block the effects of substance P, are effective in more persistent states such as postsurgical pain. Persistent pain can also alter the function of the large diameter Aβ touch afferents, ranging from increased tactile sensitivity in inflammatory conditions to frank allodynia following nerve injury or focal nociceptor stimulation. Recent advances in evaluation of supraspinal pain processing in humans have demonstrated pain-related activation using both methods that assess synchronized neural activity and methods that infer this activity in the whole brain by local changes in regional cerebral blood flow. These methods have begun to identify brain regions associated with the multiple dimensions and processing of painful stimulation and the modulation of these processes by pharmacological agents and non-pharmacological interventions.

Key words: Nociceptors; Aβ fibers; central sensitization; supraspinal pain processing.

PAIN is a complex sensory and motivational experience. The formal International Association for The Study of Pain (IASP) definition: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or both" (1), emphasizes the complexity and the loose association with physical events. At the extremes, pain can be experienced in the absence of any demonstrable physical cause, and massive damage can evoke little pain. The definition also implies that pain is foremost an experience. This experience is private, and its presence can only be communicated through linguistic descriptions of this experience. Many are naturally uncomfortable with reliance on verbal reports of pain, and partly as a consequence pain is also inferred from behavioral and physiological measures, some of which will be considered here.

The field of pain measurement has grown rapidly in the past decade. This growth has been partly in response to increased appreciation of the complexity of pain processing. Pain can be modulated at peripheral, spinal and supraspinal levels, and the nature and number of these processes change with time. Recent studies have focused on these changes during and after an injury. It is now clear that persistent pain is qualitatively different from acute pain, and that pain from an intact nervous system that correctly signals tissue injury is different from pain resulting from damage to this nervous system.

This paper will focus on the use of experimental pain to assess the complexity of pain processing and the analgesic modification of this processing, and recent advances in imaging of brain physiology related to pain. It addresses more the "what" of persistent pain, than the simple "how to measure it".

Experimental measures of pain processing

Evaluation of nociceptor mechanisms

Two classic measures of the subjective response to painful stimulation are shown in Fig. 1. The top panel shows an example of a pain threshold, the minimal amount of physical stimulation sufficient to evoke a pain sensation. The bottom panel shows a psychophysical function describing the probability of a pain sensation produced by a random series of near-threshold stimuli. Both of these methods imply a simple

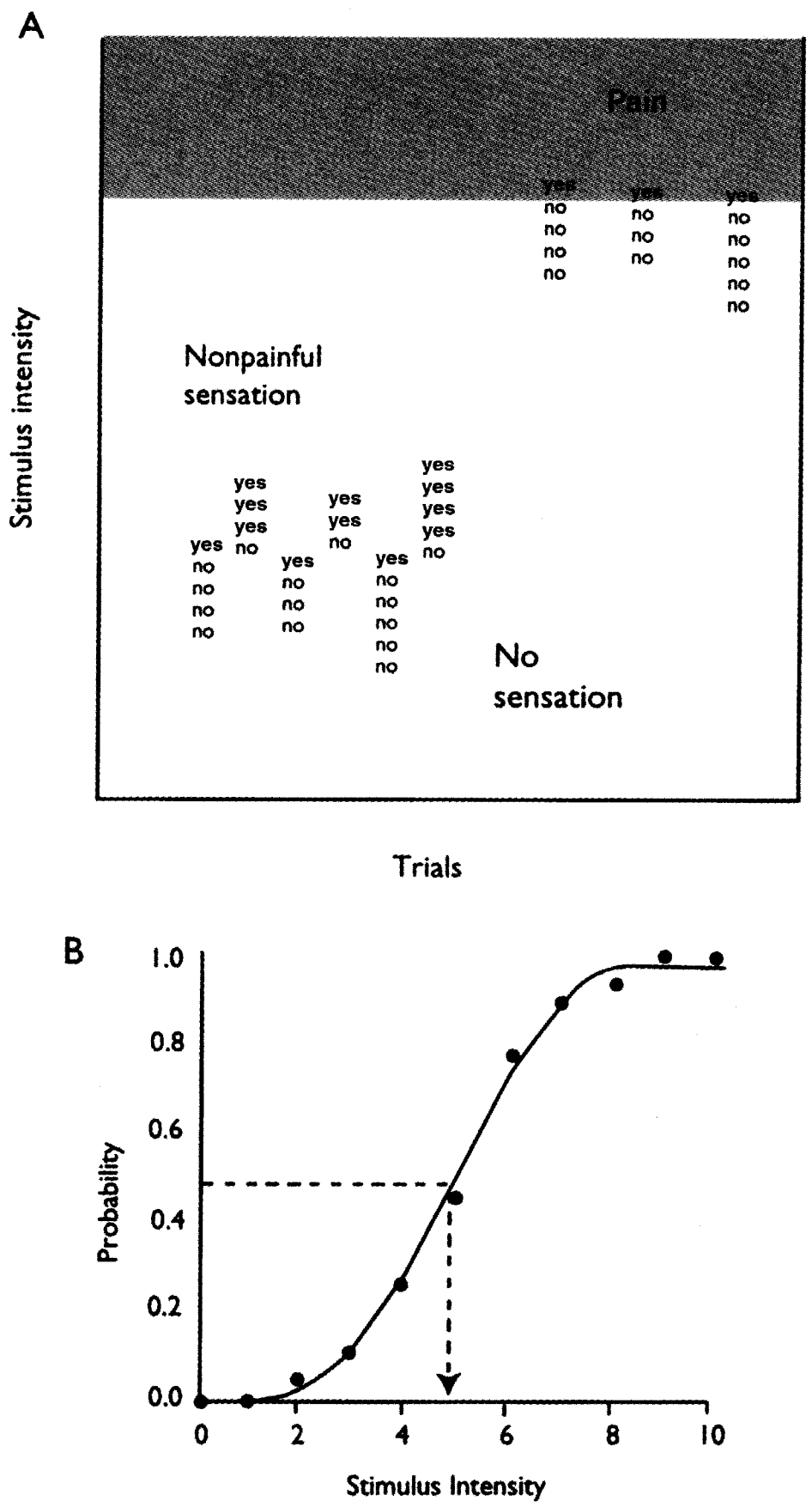
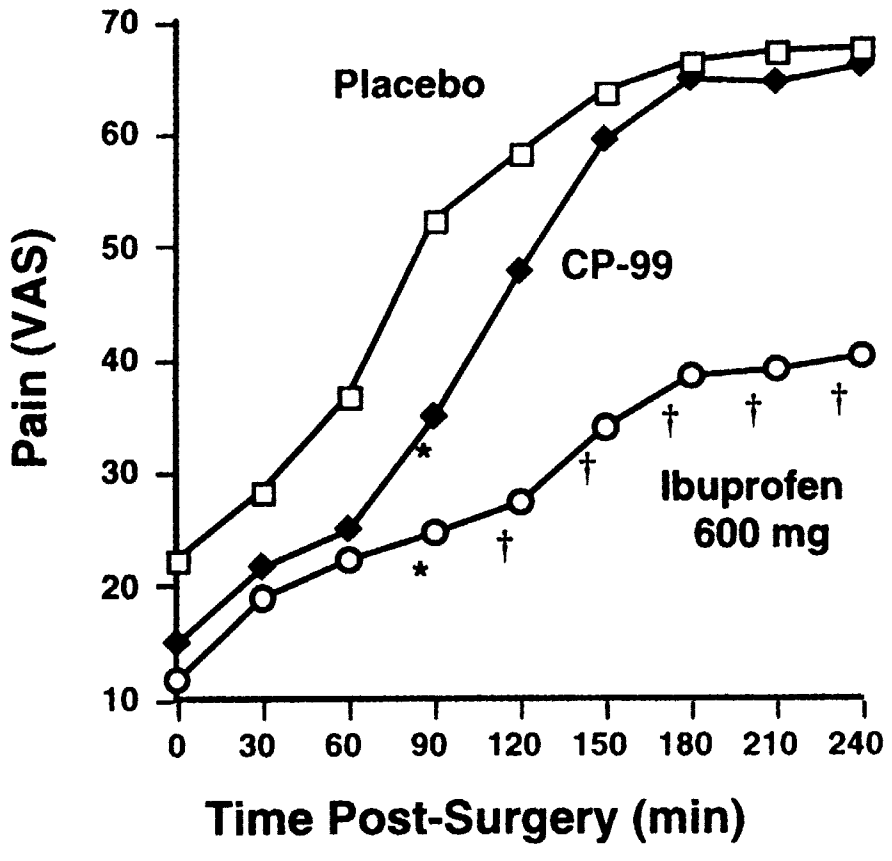


Fig. 1. Comparison of detection threshold and pain threshold. Increasing stimulus intensity results in a transition from no sensation to a non-painful sensation, and at higher levels, to a pain sensation. Thus, a detection threshold is a judgement of "stimulus present" while a pain threshold is a judgment of the attributes of a sensation that is always present. The top panel shows examples of measuring these thresholds using the Method of Limits. The bottom left shows the evaluation of detection threshold. Stimulus intensity is increased in successive discrete presentations in trial 1 until a positive response (yes) is made. Intensity is decreased in trial 2 until a negative response (no) is made. Several trials are run with varied initial starting intensities. The threshold is defined as the mean of the response transitions for each trial. A common modification of the Method of Limits to measure pain threshold is shown at the upper right of the top panel. Only ascending series are used to avoid excessively painful stimulation. The bottom panel shows an example of the Method of Constant Stimuli, in which a range of stimulus intensities about the threshold are presented in random sequence. The graph shows the probability of a positive response over stimulus intensity. The threshold is defined as the stimulus intensity corresponding to a specific response probability (in this case 0.5). This method emphasizes that the transition between no sensation, non-painful sensation and pain sensation, shown in the top panel, is not distinct and varies over trials.

fixed relation between physical stimulation and the resulting sensation and feeling state. Unfortunately, a vast amount of accumulating evidence indicates that this is not the case. The relation between pain and physical stimulation shown in Fig. 1 can be influenced by mechanisms at the level of the primary afferent at the pain receptor, axon and dorsal root ganglion. Once entering the spinal cord, the input can be modulated up or down, or change character.

The multiple processes that modulate nociceptive input can be examined by a variety of approaches. Several of these are illustrated by the studies of Brennum et al. (2–4), who evaluated the influence of pharmacological treatments on a large number of experimental pain measures. In these studies, 4 mg epidural morphine raised the pain threshold for slowly increasing stimulation by pressure, heat pain (and cooling), and increased the tolerance to pressure, thermal, and electrical stimulation (4). Ratings of pain evoked by brief, discrete electrical (1 ms), mechanical (20 ms) and laser (200 ms) stimuli were not altered by morphine. Using the same stimuli in a different study, these investigators found that epidural lidocaine had the opposite effect, attenuating the ratings of the brief discrete stimuli with little effect on the other measures (2). The authors concluded that morphine inhibits central integration of prolonged stimuli, with little effect on brief stimuli, while lidocaine is effective for brief stimuli, but is partially countered by central integration mechanisms. Thus, stimulus characteristics alone are sufficient to influence mechanisms of pain processing as revealed by efficacy of standard analgesic agents.

New analgesic treatments are designed to attenuate specific components of pain processing. Experimental methods that evaluate multiple pain components can be used to assess the analgesic profile of a putative treatment. For example, we assessed the action of a substance P antagonist in two companion experiments. These studies defined four different pain conditions. The first three were experimental conditions of the selective activation of 1): Aδ heat nociceptors, and of C-fiber nociceptors under 2): normal conditions and 3): conditions of wind-up or C-fiber temporal summation (5). The last condition was 4): postoperative pain following extraction of a third molar tooth, a controlled clinical condition involving inflammation and tissue injury (6). In the experimental pain study, the opioid fentanyl significantly attenuated the intensity of pain sensations evoked by C-fiber stimulation under normal conditions and under conditions that evoked wind-up. Fentanyl also reduced Aδ-mediated pain sensations, although this effect was



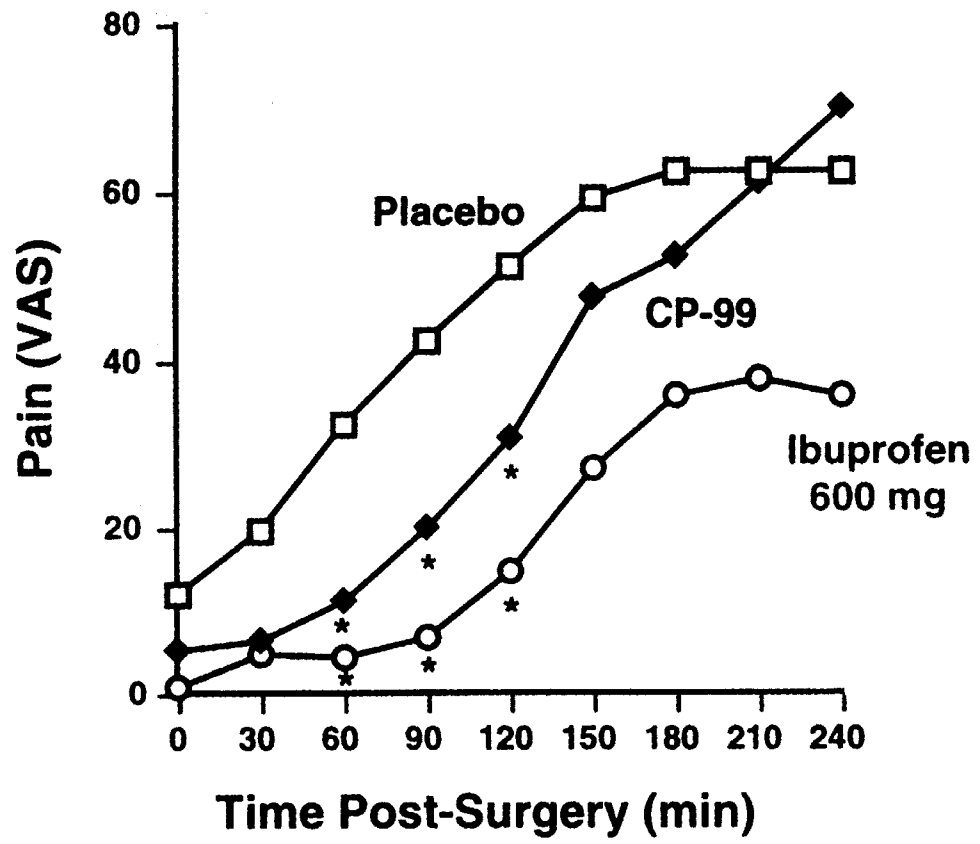


*Fig. 2. Results of ibuprofen, substance P antagonist and placebo on postsurgery pain after extraction of third molar teeth. In two independent studies, pain intensity was measured by visual analog scale (VAS) after the end of surgery (time 0) for the 3 treatment groups. Upper panel, First study: * P<0.01 versus placebo; P<0.05 versus placebo and CP-99. Lower panel, Second study: * P<0.05 versus placebo (6).*

less robust. In contrast, the antagonist CP-99,994 was indistinguishable from placebo on all of the experimental pain measures. However, Fig. 2 shows that the antagonist significantly reduced ratings of postoperative dental pain. Thus, these studies presented a continuum of pain stimulation from brief, localized to longer, diffuse conditions that evoke spinal temporal summation mechanisms, and finally conditions that evoke both spinal summation mechanisms and additional processes associated with tissue and nerve injury and with inflammation. Similar to the results of Brennum et al. (4), opioids were the least effective for the brief stimuli at the beginning of the experimental pain continuum. This result has been found in other animal and human studies that selectively activated Aδ or C-fiber afferents by instructions to selectively attend to a particular sensation (7), by varying the rates of slow thermal ramping stimuli (8), or in experimental conditions in which Aδ pain is suppressed (9). In contrast to the opioid-induced analgesia, the substance P antagonist was not effective for any experimental pain stimuli, including those delivered under conditions that evoke wind-up. However, the addition of the components of nerve injury, tissue injury and postoperative inflammation initiated further processes that were at least partly attenuated by blockade of the effects of substance P released from the nociceptive terminals.

Evaluation of the variable role of Aβ touch fibers in pain processing

Patients with a variety of pain disorders including nerve injury often present with the striking syndrome of mechanical allodynia. Lightly brushing the skin is extremely painful. A decade ago it was unclear whether this pain to light touch was due to sensitized nociceptors (10) or to altered central processing that translated the input from touch fibers into a pain sensation. While nociceptor sensitization is always possible, the accumulated evidence indicates that most cases of clinical allodynia are due to the latter mechanism. In these pathological conditions, activity in the large diameter Aβ low-threshold mechanoreceptor (Aβ-LTM) primary afferents that mediate the sense of touch evokes pain (11).

Aβ-LTM afferents can be stimulated by calibrated monofilaments (von Frey hairs) or by stroking the skin with a small camel hair brush, gauze, or similar material. At the threshold for detection, electrical stimuli selectively activate Aβ axons, and thus the evoked tactile sensations also are Aβ mediated. Electrical stimuli are particularly useful in this regard since they bypass receptor mechanisms. Touch stimuli can identify the presence of allodynia but cannot identify the mechanism. Pain evoked by normally innocuous electrical stimulation strongly suggests that the allodynia is mediated by Aβ fibers.

Evaluation of central sensitization and progressive tactile hypersensitivity

A large body of evidence, some discussed in the next section, indicates that Aβ-mediated allodynia is one consequence of the altered central processing termed

central sensitization. Other symptoms include spontaneous pain and pinprick hyperalgesia. Central sensitization can be produced experimentally by a number of methods. The tissue damage following an experimental burn is a classical method (12). Recent studies have used intradermal injections or topical applications of capsaicin, the pungent ingredient in chili pepper. This method has the advantage of producing central sensitization without the tissue damage produced by a burn injury. Administration of capsaicin has been considered to activate nociceptors without any damage, although recent studies have identified a reversible superficial dennervation associated with capsaicin administration (13).

A burn or injection of capsaicin often results in two concentric areas of altered sensation in adjacent tissue not directly affected by the intervention. These "secondary areas" include an area of mechanical allodynia and a usually larger area of mechanical hyperalgesia to punctate stimuli such as a pinprick. In each case, these secondary areas are assumed to result from altered central processing of otherwise normal afferent input due to central sensitization of spinal neurons by the nociceptive input from the noxious capsaicin or burn stimulus.

In addition to the mechanical allodynia found with central sensitization, Aβ-LTM afferents have also been implicated in altered sensory functioning that accompanies post-injury inflammation. Animal studies have revealed lowered Aβ detection and pain thresholds, and have shown that further increases in persistent Aβ stimulation results in increased sensitivity (14).

Components of this "progressive tactile sensitivity" (14) have been evaluated in a recent human study in our laboratory (15). In this study, we performed extensive sensory testing in several orofacial regions before and 2 and 8 days after oral surgical removal of a single lower third molar tooth. Testing was performed in the terminal territory of the inferior alveolar nerve (mental nerve) involved in the extraction, and in the terminal territory of the adjacent lingual nerve which branches proximally from the inferior alveolar nerve. At 2 days post surgery at the peak of postoperative inflammation (16) the inferior alveolar nerve is assumed to be both mechanically injured and inflamed, while the lingual nerve is assumed to be inflamed with only minimal mechanical trauma.

The results of Aβ tests using 10 Hz electrical stimulation are shown in Fig. 3. Increased Aβ sensitivity (lowered electrical detection thresholds) was observed in both the mental and lingual nerve territories, a result observed with 100 Hz electrical stimulation and with mechanical stimulation (not shown). These decreased thresholds indicate an increased sensitivity in Aβ-LTM afferents which are selectively activated by the electrical and mechanical stimuli. In contrast, Fig. 4 shows the detection thresholds to warm and cool stimuli, which were unchanged by inflammation.

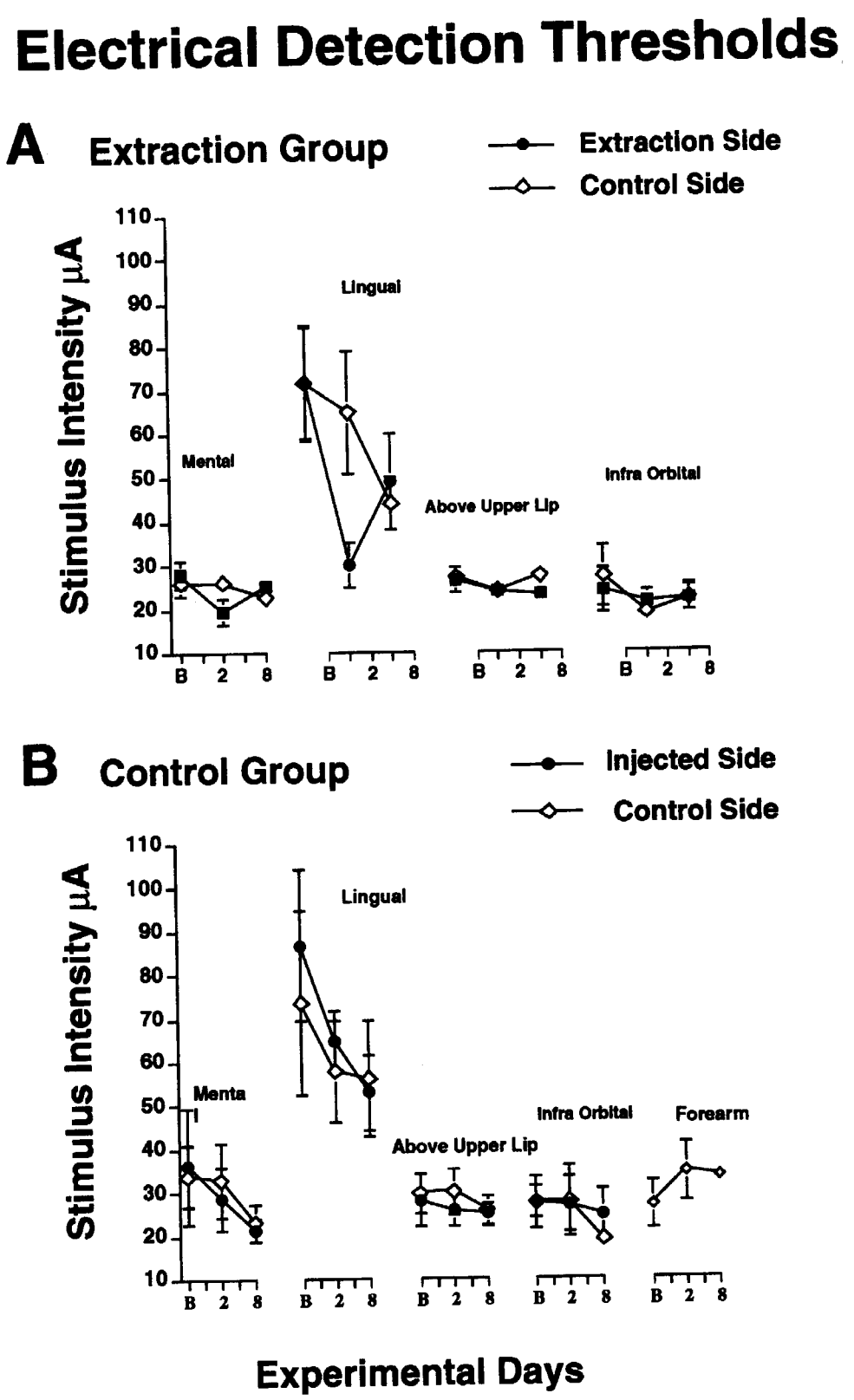


Fig. 3. Electrical detection thresholds to 10 Hz stimulation following extraction of a lower third molar tooth. The top panel shows the results of the extraction. Stimulus current (mA) and standard errors are plotted against days (pre-operative baseline and 2 and 8 days post surgery) for the mental, lingual, cutaneous upper lip and infraorbital nerve territories. In comparison to the control side, detection thresholds were significantly lower ($P<0.05$) on the extracted side 2 days after surgery for both the mental and lingual nerve territories at both stimulus frequencies. The bottom panel shows electrical detection thresholds for a control group receiving a local anesthetic block of the descending mandibular branch of the trigeminal nerve. Stimulus current (mA) and standard errors are plotted against days (pre-operative baseline and 2 and 8 days post injection) for the mental, lingual, cutaneous upper lip and infraorbital nerve territories. In comparison to the control side, detection thresholds were unaltered on the injected side at any time or location.

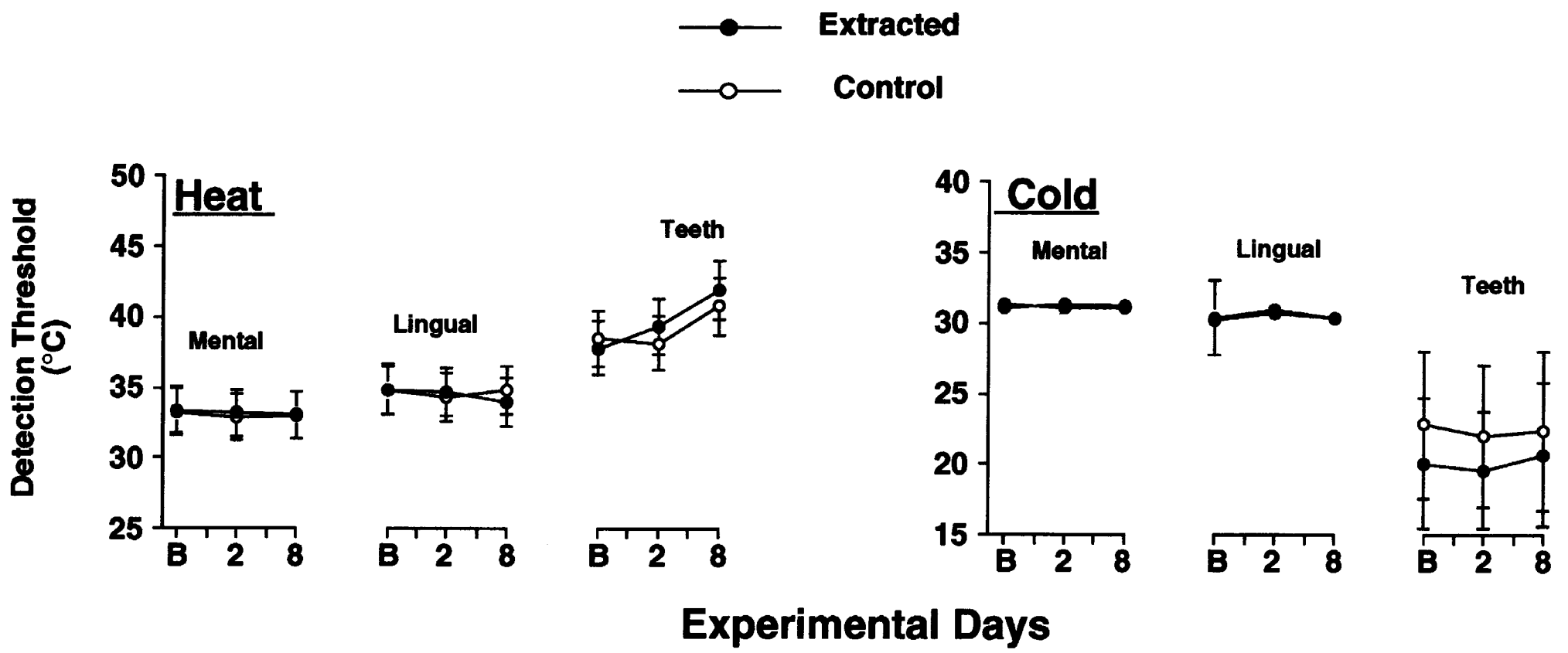


Fig. 4. Thermal detection thresholds following extraction of a lower third molar tooth. Detection thresholds (°C) are plotted against days (pre-operative baseline and 2 and 8 days post surgery) for heat, shown on the left, and for cold, shown on the right. Each panel shows thresholds and standard errors for the mental and lingual nerve territories and for the first intact premolar tooth on both the extracted side and the contralateral control side. The horizontal dashed line shows the base temperature of 32°C. There was no significant difference between sides at any location.

These unchanged thresholds indicate that the sensitivity of the smaller Aδ and C fibers was not altered by the assumed postoperative inflammation. This selective increase in Aβ sensitivity observed in human subjects is one feature of progressive tactile sensitivity observed in animal studies. The additional feature of Aβ-mediated pain sensation was also observed; pain thresholds to electrical stimuli were decreased, suggesting a switch from pain evoked by Aδ nociceptors to pain mediated by the Aβ fibers, which are activated at current strengths less than the currents required to activate Aδ fibers.

A number of Danish investigators have used the classic burn model to assess the effects of a wide array of interventions on the symptoms of central sensitization. Using controlled burn injuries to the calves (15×25 mm 49°C contact thermode applied for 5 min) these investigators showed that administration of the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen reduced only the magnitude of motorized brush-evoked allodynia, indicating an attenuation of inflammation-produced progressive tactile sensitivity, but no effect on the underlying central sensitization (17). In contrast, both preemptive and post-injury morphine reduced pain sensitivity to heat within the area of injured skin, and also reduced the extent of allodynia and pinprick hyperalgesia surrounding the burned region (3). This pattern of results suggests that morphine reduced the nociceptor input maintaining the central sensitization (3). Blocking this input by administration of preemptive local anesthetics can delay the onset of central sensitization (12), while administration of nerve blocks also reduced the magnitude of the subsequent primary and secondary hyperalgesia (18). The consequences of the maintaining of nociceptive input have been evaluated by treatments that target the *N*-methyl-D-aspartate (NMDA) receptor, which has been shown to be intimately involved in the mechanism of central sensitization. The NMDA antagonist ketamine also reduced the magnitude of primary and secondary hyperalgesia and the pain to prolonged heat stimulation. Unlike the effect observed after morphine, ketamine likely attenuated the consequence of persistent input since it had no effect on pain evoked by brief heat stimulation (19). The NMDA antagonist dextramethorphan was less potent, reducing only the magnitude of pinprick hyperalgesia (20).

A number of studies have evaluated the influence of the sympathetic nervous system on the sensory consequences of central sensitization produced by capsaicin. The action of sympathetic agonists, achieved by either stimulation of endogenous noradrenaline or administration of exogenous noradrenaline, has been shown to enhance thermal hyperalgesia (21, 22). Liu et al. (23) found that the alpha adrenergic antagonist phentolamine decreased the extent of mechanical allodynia with no effect on the extent of mechanical punctate secondary hyperalgesia. These results provide further evidence that altered sensi-

tivities to Aβ and to nociceptor input are mediated by independent mechanisms.

Capsaicin has also been used to assess the influence of the NMDA receptor in central sensitization. Park et al. (24) found that the extent of capsaicin-produced mechanical allodynia was attenuated after administration of ketamine, a result consistent with the effect of ketamine on experimental burns (19) or with clinical cases of neuropathic pain (25).

Supraspinal pain processing

In the latter part of this decade there has been both increased studies of supraspinal pain processing using established methods, and continued development of new methodology. These methods provide a continuum of procedures that vary in temporal and spatial resolution, and inferential power.

Cortical evoked potentials

Beginning with the initial study by Carmon et al. in 1976 (26), the method of cortical evoked potentials has been used to assess the brain response to painful stimulation. Measures of cortical activity evoked by brief electrical or laser stimuli include both the amplitude and latency of prominent positive and negative peaks. These measures have been shown to co-vary with the magnitude of the evoking stimulus, and also with the magnitude of subjective measures of pain intensity (27–29). More recent studies have examined the character and topography of potentials evoked by stimulation applied to different body regions (30–33) or to selective classes of primary afferents (34).

A number of studies show that the amplitudes of specific peaks of the cortical evoked potential waveform are attenuated following administration of analgesic interventions (35–38). In these situations, measures of evoked potentials show the same effects observed with verbal reports. Depending on the point of view, this similarity in response can indicate that the physiological measure can supplement, if not replace, verbal measures. For those uncomfortable with the subjective nature of verbal reports, these studies suggest that measures of evoked potentials may provide a more objective measure of pain magnitude that is not influenced by the biases that can influence "subjective" verbal judgement. This notion is appealing and has been shared by previous studies that sought an objective, physiological measure of pain. Unfortunately, previous attempts have failed due to the lack of both sensitivity and specificity. Similarly, modern measures of evoked potentials can be altered without changes in reported pain (28, 39, 40–43). Innocuous interventions such as movement can reduce the magnitude of the evoked potential without altering verbal report (44). Thus, like verbal reports, evoked potentials can be influenced by a number of biasing factors. These methods have not been developed sufficiently to replace verbal reports, and few studies use these measures alone. In fact, evoked potentials and other physiological measures are validated by comparing them to verbal judgements of pain magnitude. This implicitly elevates subjective judgement to the level of a validational standard. This leads to the obvious question of why we need physiological pain measures when the validity criterion (verbal report) is available.

One reason is that reliable verbal report may not be available in specific situations, such as in infants or children, in adults with poorly developed or impaired language skills, or in situations such as general anesthesia. Another reason is that physiological measures can contribute to pain measurement by providing an independent measure that can be compared to verbal reports. Similar effects on verbal and physiological measures would increase the confidence in an observed effect. However, a lack of correspondence does not necessarily invalidate an experiment. If reliable, such a difference may provide information about the influence of the intervention on what is now recognized as a complex, multi-stage system of pain processing. For example, Meier et al. (43) observed that hypnosis resulted in decreased verbal pain ratings but no change in the cerebral potential evoked by intracutaneous electrical stimulation. This difference between verbal report and evoked potentials was attributed to the multidimensional aspect of pain. Evoked potentials were assumed to be an analog of verbal reports of sensory intensity. The observed differences between subjective measures and the magnitude of evoked potentials was attributed to a change in only the unpleasantness dimension which was reflected in reduced verbal judgements but did not alter the sensory-discriminative component which is assessed by evoked potentials. The reader can appreciate that the validity of this interpretation or the validity of evoked potentials rests on the reliability of the effect and its congruence with known mechanisms of supraspinal pain processing and of pain report. A recent group of articles in *PAIN FORUM, Vol 7, No 4, 1998* address these issues in detail.

Functional brain imaging: Positron Emission Tomography (PET)

Recently there has been a tremendous growth in studies that use changes in glucose utilization or changes in regional cerebral blood flow (rCBF) to as-

sess changes in neural activity throughout the entire brain. Evaluation of labeled glucose assesses the local energy requirements of neural structures and increases with an increase in neural activity. rCBF methods are more indirect. A focal increase in neural activity results in localized increases in blood flow to meet the oxygen demand at the locus of increased neural activity. In each case, the increase in glucose utilization or in rCBF can be detected and measured in 3-dimensional space, resulting in a measure of neural activity in a portion or in all of the brain. Subtraction measures obtained during different conditions result in a measure of brain activity associated with the functional difference between these conditions.

A typical PET experiment involved intravenous infusion of a radioactive tracer such as H2015 every 10 min for 6–8 scans. Each scan lasted from 60 s to 90 s after the injection. In many of these first studies brief repetitive heat stimuli were delivered at painful intensities during some scans and at nonpainful hot intensities during control scans (45–52). Subtraction of the control scans from the painful scans removed the effects of nonpainful heat and also the effects of mechanical stimulation if a contact thermode was used. The resultant 3-dimensional image of changes in rCBF was assumed to represent activity associated with pain processing.

In practice, this analysis involves a number of processing steps including global intensity normalization and spatial smoothing. Processed volumes for each condition are transformed into standard space. For each discrete unit of each volume (voxel) the two conditions are compared over a group of subjects with statistics such as a paired *t*-test.

A group of brain structures is consistently activated by brief heat stimuli, including the anterior cingulate cortex, primary and secondary sensory cortex, thalamus, insula and lentiform nucleus. The degree of activation in some of these structures has been shown to be related to stimulus intensity or to subjective magnitude of the evoked pain sensations (51, 53). The consensus from these studies suggests a pattern of activation that may be related to painful stimulation by brief stimuli. Future studies are needed to assess the specificity of this effect. A pain-specific effect would be a major advance, providing a physiological correlate of supraspinal pain processing. New methodology also allows as many as 32 scans in a single person. With this technology future studies can also assess the degree to which the observed group pattern is found in individual subjects. For example, such studies may identify separate subgroups that together form the observed group patterns of activation.

It is important to note that the outcome of the above studies will be limited to the use of brief stimulation until their relevance to clinical pain has been established. Several studies have addressed the relevance of studies using brief stimulation by delivering tonic stimulation that persists throughout the duration of the scan. In these studies, pain produced by intradermal injection of capsaicin, by injection of ethanol or by prolonged heat or cold, have shown similar patterns of activations as those produced by repetitive brief stimuli (54–59). These results provide converging lines of evidence that the patterns of activation observed in PET studies generalize to stimulation, either constant or repetitive, that lasts for the duration of the scan. However, studies of clinical pain have also observed distinctly different activations, such as decreased activity in the contralateral thalamus (60). Several mechanisms could account for such decreased activity. The decreased activity during chronic pain could represent the activation of tonic inhibitory systems that dampen input at spinal and thalamic levels. Alternatively, decreased activity could represent a tonic phase of neural activation that is relatively more efficient, in terms of energy demands, than phasic activation associated with experimental stimulation. An additional possibility is that the correspondence between neural activity and rCBF breaks down during chronic stimulation, with decreased regional flow to the same magnitude or neural activation.

A recent study in our laboratory addresses the difference between brief experimental pain and prolonged clinical pain by comparing the response to painful repetitive heat stimuli to the response of prolonged pain produced by tourniquet ischemia (61). Subjects received repetitive 5-s painful (49°C) or warm (35°C) heat stimuli during separate scans. They then squeezed a hand dynamometer in a controlled manner after blood flow had been occluded by a tourniquet inflated to 200 mmHg. Three PET scans were delivered at 0, 10 and 20 min after cuff inflation, and a final scan was delivered after cuff deflation. In a preliminary analysis of 8 subjects, the painful heat stimuli activated a number of regions found in similar studies, including primary and secondary sensory cortex, anterior cingulate cortex and insular cortex. In contrast, the prolonged pain from tourniquet ischemia (rated as equally intense and more unpleasant than pain evoked by 49°C) did not cause increased activity in any of these regions.

This result with prolonged tourniquet ischemia is consistent with the results observed with chronic pain, but does not distinguish between the possible interpretations. This result also suggests an ad-

ditional, cognitive interpretation. Previous PET studies using either brief or tonic stimuli share many cognitive features. Subjects receive an episode of pain that is coincident with the scan. Subjects expect this painful episode, are free to employ coping strategies for this short duration of pain, and know that the pain will terminate. In contrast, during the ischemia condition scans occurred at 10-min intervals during the continuous pain; there was no change in condition during the scan times.

More recent studies have examined cognitive factors by manipulations of attention and by hypnotic suggestion. Instructions to attend to one of two simultaneous stimuli (auditory or thermal) influenced PET activation in the primary sensory cortex (62). Similarly, a recent functional Magnetic Resonance Imaging (fMRI) study showed that instructions to attend to the pain produced by a pressure stimulus modulated activation in the anterior cingulate cortex (ACC) and insular cortex (63).

The results of several studies suggest that processing affective aspects of pain is one of the many functions of the ACC. This role of the ACC is consistent with recent experiments in which hypnotic suggestion was used to selectively reduce pain intensity (64) or pain unpleasantness (65). The results of these studies are consistent with previous models of pain processing in which an affective system serves as an amplifier with variable gain that receives the magnitude of pain sensation as an input (66). Hypnotic suggestion directed towards reduced pain intensity resulted in an attenuation in the activation primary sensory cortex. In contrast, hypnotic suggestions of either increased or decreased unpleasantness of pain sensation resulted in the appropriate increase or decrease of both unpleasantness ratings and of activation in the ACC.

These examples have gone beyond the demonstration of pain activations to the evaluation of differences due to different types of evoked pain and the effects of interventions that modify evoked pain. In addition to the hypnotic interventions described above, at least two studies have examined the effects of conventional analgesic agents. Gyulai et al. (67) found that nitrous oxide increased rCBF in the contralateral infralimbic and orbitofrontal cortices, and abolished the pain-evoked activation of anterior cingulate, thalamus and supplementary motor area. Adler et al. (68) showed that the potent opioid fentanyl increased activation in the ipsilateral prefrontal cortex and in the contralateral supplemental motor area. However, in contrast to nitrous oxide, fentanyl did not attenuate any pain-evoked activation.

The fact that a potent, standard analgesic did not reduce any pain-evoked activation is a critical finding that should be explored in future studies. Analgesics are bound to exert multiple effects independent of pain attenuation. Such effects need to be well characterized. These caveats also apply to previous studies delivering painful stimulation. For example, intradermal capsaicin produces an extremely intense pain sensation that activates the same group of structures activated by brief painful stimuli such as heat. Replication by a fully quantitative study using arterial sampling has shown that capsaicin also dramatically alters total cerebral blood flow (69). Such an effect could too easily lead to spurious results. In this case, this general effect did not obscure the pattern of results, since similar effects were observed in the quantitative study. However, such global changes or other "side effect" changes can easily result in a confounded effect in other situations. Since necessary findings such as stimulus–response functions have been demonstrated only recently (69), the interpretation of analgesic interventions must proceed with caution until a sufficient body of evidence has verified findings and identified unrelated confounding effects. This caveat is not unique to PET but rather applies to all evaluations of analgesic interventions. For example, cortical evoked potentials have been modified by various interventions including painful stimulation, cooling of the extremities, or baroreceptor stimulation (70–72).

Functional Magnetic Resonance Imaging (fMRI)

Magnetic Resonance Imaging (MRI) uses the intrinsic magnetic properties of molecules to produce highly detailed images that distinguish between soft tissues such as neuronal cell bodies, myelin, cerebrospinal fluid, and bone. MRI has become a dependable tool for evaluation of anatomical disorders and has recently been used to assess neural function as well as structure. Functional MRI (fMRI), like PET, infers neural activity from changes in rCBF. fMRI can use injected tracers, although the most popular method uses an intrinsic signal from blood to produce images of neural function. An increase in localized neural activity signals an increase in rCBF that overcompensates for the oxygen demand. The level of oxygen in the blood provides a signal since oxygenated hemoglobin has neutral magnetic properties while deoxygenated hemoglobin has magnetic properties that interfere with the signal from adjacent tissue. Neural activity results in a relative increase in local oxygen, which reduces local interference resulting in an increased signal from the local tissue. This increase, small com-

pared to the signal in PET studies, is usually about 1% or 2%. Thus, signal averaging methods must be used to obtain a usable signal-to-noise ratio. This translates into many trials that must be averaged or statistically compared to achieve a meaningful result. Because of possible slow drifts in scanner sensitivity, the experimental conditions must be alternated to control for such temporal confounds.

fMRI has several advantages over PET imaging. fMRI requires no exposure to ionizing radiation. Thus, there is less adverse risk per subject and, unlike PET, subjects may be scanned repeatedly. fMRI also has a much greater temporal and spatial resolution. PET images of the entire head are usually obtained in the order of every 10 min, and newer scanners can reduce this time to 6 min with less sensitivity. In contrast, fMRI can obtain entire head images in 1–4 s. fMRI may also obtain a resolution of less than 1 mm, while the minimal PET resolution is 4–6 mm, depending on the direction of the dimension.

fMRI has just recently been applied to the evaluation of supraspinal pain processing. Painful stimulation by cold has revealed activity in ACC using a low power clinical scanner (73). The low resolution of PET has made it difficult to localize near-midline ACC activations. Davis et al. (74, 75) used painful electrical nerve stimulation and the available increased spatial resolution to show that near-midline activation of the ACC was actually a contralateral activation in a region posterior and inferior to ACC activation from an attention task. Electrical stimulation of the mastoid has revealed bilateral activation of thalamus and insular cortex (76), and electrical stimulation of the palm and fingers has revealed activation in the central sulcus (77). Painful heat has revealed activations in the same areas shown in PET studies (78–80). Interestingly, individual analyses showed a strong activation of secondary somatosensory cortex by heat (81) but a group analysis did not show these activations (78).

An increasing number of laboratories are using fMRI to assess supraspinal pain processing. These studies can take advantage of the increased temporal and spatial resolution, the ability to analyze results in single subjects, and the ability to repeatedly assess specific individuals. However, it should be emphasized that there are still unique uses for PET. Because of the need to control for drifts in sensitivity and the need to average trials, fMRI may not be the first choice for certain experimental designs. Examples are AB designs in which the intervention (B) can only be administered once in the session (e.g. capsaicin injection, or anticipation of a novel stimulus). In addition, PET methodology can uniquely quantify receptor function by ligand binding studies.

Source analysis of evoked activity

Neither PET nor fMRI can provide images of activity that occurs within a fraction of a second. Source analysis from cortical evoked potentials can be used to assess events within this window (82, 83) and have been shown to identify activity in primary and secondary sensory cortex and in the ACC (84). Evoked potentials have also been recorded directly from the surface of the cortex, identifying a strong contralateral, and weak ipsilateral, response from the ACC and supplemental motor area produced by stimulation of the face with a CO_2 laser (85). The electrical currents generated by neural activity may also be assessed by the magnetic fields generated by variation in these currents. Using a number of extremely sensitive super-cooled detectors, the resulting magnetic signals can be subjected to a source analysis to localize the regions that generated the neural activity. The method of mangnetoencephalography (MEG) has demonstrated activity in secondary sensory cortex during electrical toothpulp stimulation (86) and more recently demonstrated bilateral activity in primary and secondary sensory cortex following electrical stimulation of the finger (87). This study also revealed a temporal sequence that could not be observed with techniques such as PET. The stimulus results in an initial response in primary sensory cortex followed by intermittent bilateral responses in both primary sensory cortex and in secondary sensory cortex and nearby insular cortex.

Although apparently similar, the methods and caveats for source modeling with EEG and MEG methods are different and these methods possess different strengths and weaknesses. Thus, a complementary approach using both methods is optimal (82).

Electrophysiological recording from human brain

Direct measures of activity from individual neurons can be obtained during stereotactic neurosurgical procedures. In addition, the subjective consequence of stimulating isolated neurons may also be investigated. Stimulation in areas posterior and inferior to the principal sensory nucleus of the thalamus (Vc) can evoke sensation of warmth, heat and pain (88). In published cases, stimulation has produced an entire experience of previous visceral pain such as pain from the appendix (74) or angina (89, 90). These results suggest a limbic-cortical memory system for pain similar to that for other sensory systems (91).

Conclusion

This paper highlights a sample of recent methods used to evaluate pain and pain mechanisms in human subjects. It focuses on psychophysical studies delivering controlled painful and nonpainful stimuli, and on assessment of supraspinal pain processing. Decades ago, pain was considered to be a fairly simple construct measured easily with simple methods. As our understanding has grown it is now clear that the experience of pain results from a number of interconnected systems, which can change character over time. Measurement methods have and continue to evolve to meet this complexity with an expanding portfolio of procedures that assess the chain of events from receptor to conscious expression, and the modification of this system after injury or in disease states.

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